ABC proteins as transport modifiers

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Maire Egan (*New Haven, Connecticut, USA*) introduced the ROMK channel family, which are renally-derived ATP-sensitive K^+ (IKATP) channels. In renal tissue IKATP channels are present in the apical membrane of distal nephron segments where they play a major role in K^+ homeostasis. One of the ROMK isoforms, ROMK2, is functionally similar to the "native" small conductance ATP-sensitive K^+ channel of the cortical collecting duct and the thick ascending limb nephron segments. However, unlike the native channel, which is sensitive to sulfonylureas, ROMK2 exhibits only low and highly variable sensitivity to sulfonylurea compounds such as glibenclamide. The cystic fibrosis transmembrane conductance regulator (CFTR) is a member of the ABC superfamily, which is highly expressed in the nephron. Its distribution in the nephron overlaps with the distribution of ROMK. CFTR confers sulfonylurea sensitivity to ROMK channels. Only specific domains of CFTR are involved in the ROMK/CFTR interaction. Nucleotide binding domain 1 and the regulator domains are necessary for the ROMK2/CFTR interaction. In contrast, NBF2 and TMD2 are not essential. The effects of phosphorylation on this interaction also have been examined. In conditions that promote phosphorylation, the ROMK2/CFTR interaction is attenuated. Studies are being performed in epithelial cells to determine if these interactions are important in native tissue (abstract; McNichols et al, *J Am Soc Nephrol* 7:A0195, 1996) [1].

Several ABC transport proteins function as regulators of other proteins. Lydia Aguillar-Bryan (*Houston, Texas, USA*) explained that this phenomenon is well known for the sulfonylurea receptors, SUR1 or SUR2, members of the ABC-superfamily that regulate ATP-sensitive potassium channels. For example, the combination of inwardly rectifying, ATP-sensitive K^+ channels, KIRs and SUR, couple metabolism to membrane electrical activity in several cell types. Loss-of-function mutations in human Sur1 (the *ABCC8* gene) or KIR6.2 (the *KCNJ11* gene) cause both recessive and dominant forms of congenital hyperinsulinism (HI), a disease characterized by inappropriately high levels of insulin for the low glucose values. The degree of hypoglycemia is life threatening in the severe forms of the disease, for example, mutations that truncate SUR1 and prevent surface expression, that respond poorly to clinical treatment and require a pancreatectomy [2, 3].

William Guggino (*Baltimore, Maryland, USA*) points out that in addition to its regulation of ROMK, CFTR regulates a number of ion channels and cellular processes including the epithelial Na^+ channel, ENaC, the outwardly rectifying Cl^- channel ORCC, the HCO_3^- transporter and ATP release mechanisms [4]. A defect in CFTR-regulated processes contributes to the multitude of symptoms in cystic fibrosis. Another important feature of CFTR is that it is localized at the apical membrane in most epithelial tissues. The apical membrane localization of CFTR presumably is a prerequisite for CFTR to regulate other apical processes. Recently, CFTR associating PDZ domain proteins are emerging as central molecules in scaffolding, targeting and regulating CFTR within macromolecular complexes. The carboxy terminus of all cloned CFTR molecules to date can be characterized as a type I PDZ binding motif (TXL). Two PDZ domain proteins, CAL and CAP70, may be involved in scaffolding, trafficking and regulating of CFTR. CAL contains one PDZ domain and two coiled-coil domains. CAP70 contains four PDZ domains. Both proteins bind to CFTR via PDZ domains. CAL is involved in the trafficking of CFTR from Golgi to the apical membrane, and CAP70 regulates CFTR channel activity at the apical membrane [5, 6].

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